Association between cumulative exposure to maternal psychological distress in the prenatal and postnatal periods and atopic dermatitis in children: Findings from the TMM BirThree Cohort Study

Master's Thesis

Association between cumulative exposure to maternal psychological distress in the prenatal and postnatal periods and atopic dermatitis in children: Findings from the TMM BirThree Cohort Study

(産前産後の母親の心理的ストレス反応と児におけるアトピー性皮膚炎の関連：東北メディカル・メガバンク計画三世代コホート調査)

Tohoku University Graduate School of Medicine
School of Public Health
Disaster Public Health

Chikana Kawaguchi

Abstract

Atopic dermatitis (AD) is a common chronic inflammatory skin disorder that is characterized by clinical features of itch and eczematous lesions. AD is likely to have negative effects on sleep, discrimination, and complexity of family relationships. Maternal mental health in the prenatal period and postnatal period has been examined as a possible risk factor for AD in children. However, no study has examined the cumulative impacts of maternal mental health in the prenatal and postnatal periods on AD in children. The aim of the present study was to examine the association between cumulative exposure to maternal psychological distress in the prenatal and postnatal periods and the development of AD in children. This study found that 43.8% of all women experienced psychological distress in the prenatal or postnatal period, and 13.9% of children developed AD between the ages of one and two years. Maternal psychological distress in both prenatal and postnatal periods was associated with an increased risk of AD in children compared to no psychological distress in both periods (odds ratio (OR), 95% confidence interval (CI): 1.41, 1.20-1.65). Maternal psychological distress in only the postnatal period was associated with an increased risk of AD in children (adjusted OR, 95% CI: 1.28, 1.06-1.54). Maternal psychological distress in only

the prenatal period was not associated with AD (adjusted OR, 95% CI: 1.15, 0.96-1.39). In conclusion, the present results demonstrate that cumulative exposure to maternal psychological distress in the prenatal and postnatal periods is associated with an increased risk of AD in children.

Keywords: atopic dermatitis, children, cumulative exposure, mothers, psychological distress

Background

Atopic dermatitis (AD) is a common chronic inflammatory skin disorder characterized by clinical features with remission and relapse of itch and eczematous lesions (Weidinger and Novak 2016). AD is likely to have negative effects on sleep, discrimination (Weidinger and Novak 2016), and complexity of family relationships (Howlett 1999; Yang et al. 2019). Moreover, allergen sensitization may lead to asthma, allergic rhinitis, wheeze, or food allergy (Weidinger and Novak 2016). The Japanese national cohort study found that AD developed during the first year of life and peaked at two years of age, such that 15.3% of 2-year-old children had AD (Yamamoto-Hanada et al. 2020).

Regarding possible risk factors for AD in children, maternal mental health in the prenatal and postnatal periods has been examined (Chan et al. 2018). Prenatal maternal mental health problems were associated with an increased risk of AD in children (Chan et al. 2018; van der Leek et al. 2020). Postnatal maternal mental health problems were also associated with an increased risk of AD in children (Wang et al. 2016; El-Heis et al. 2017; van der Leek et al. 2020). Given these results, the present study examined the hypothesis that cumulative exposure to maternal mental health problems in the prenatal and postnatal periods is

associated with an increased risk for AD in children. This hypothesis has been examined for other allergic conditions, such as wheeze and asthma (Chiu et al. 2012; Brew et al. 2018). Both studies showed that cumulative exposure to maternal mental health problems in the prenatal and postnatal periods was significantly associated with an increased risk of wheeze or asthma in children. On the other hand, no study has examined the association with AD.

Based on my experience throughout the postgraduate public health course, it appeared that many children had skin problems when I was working at the health center to collect the data for the Tohoku Medical Megabank Project Birth and Three-Generation Cohort Study (TMM BirThree Cohort Study). It was valuable experience for me, and it motivated me to explore childhood AD as the theme of my thesis. I hope this study will contribute to understanding the significance of maternal psychological distress in childhood AD.

Therefore, the purpose of this study was to examine the association between cumulative exposure to maternal psychological distress in the prenatal and postnatal periods and the development of AD in children.

Materials and Methods

Data were derived from the TMM BirThree Cohort Study, which is a prospective birth cohort study. Detailed information on the structure and aim of the TMM BirThree Cohort Study can be found in the cohort profile (Kuriyama et al. 2020). This cohort recruited eligible pregnant women and their families from 2013 to 2017 at obstetric clinics or hospitals in Miyagi Prefecture, Japan. In consequence, a total of 32,968 pregnant women and 23,730 fetuses were recruited. In the present study, among 23,730 mother-child pairs, 910 mother-child pairs were excluded due to withdrawal from participation (n = 455), abortion, still birth, or child death (n = 323), no identification of childbirth status (n = 111), and mothers under 18 years of age (n = 21). Of the remaining 21,674 mother-child pairs, 9,245 pairs who had missing data on AD and 2,453 pairs in which the child had AD at the age of one year were excluded. Subsequently, 579 mother-child pairs who had missing data on the following variables were excluded: smoking status in pregnancy (n = 241), prenatal psychological distress (n = 66), parity (n = 22), preterm birth (n = 9), low birth weight (n = 4), postnatal psychological distress (n = 153), and educational attainment (n = 84). Of 10,543 mother-child pairs, 2,062 pairs who had missing data on AD at the age of two years were excluded. Thus, a total of 8,481 mother-child pairs were analyzed in

this study (Figure 1). Characteristics of participants included and not included in the analysis is shown in the supplementary table (Table S1).

The TMM BirThree Cohort Study protocol was reviewed and approved by the Ethics Committee of Tohoku University Tohoku Medical Megabank Organization (2013-1-103-1). All participants provided their informed consent at enrollment.

In early pregnancy and one year after delivery, mothers responded to the Japanese version of the K6 scale (Kessler et al. 2002; Furukawa et al. 2008). The K6 scale consists of six questions asking about the frequency that mothers experienced symptoms of psychological distress during the past 30 days, as follows: 1) nervous, 2) hopeless, 3) restless or fidgety, 4) depressed that nothing could cheer me up, 5) everything was an effort, and 6) worthless. The responses ranged from 0 to 24 using a 5-point Likert scale for each question: “none of the time” (0 points), “a little of the time” (1 points), “some of the time” (2 points), “most of the time” (3 points), and “all of the time” (4 points). A higher total score indicates a worse mental health status. The focus of this study was on maternal mental health, in particular, a state of psychological distress described as the beginning of major depressive disorders, such as anxiety and depression (American Psychological Association 2020). It was defined as a K6 score ≥ 5,

which is used to indicate psychological distress, including mood/anxiety disorders (Sakurai et al. 2011). Maternal psychological distress was categorized into four groups based on previous studies (Mora et al. 2009; Sutter-Dallay et al. 2012; Rotheram-Fuller et al. 2018); no psychological distress in both prenatal and postnatal periods; psychological distress in only the prenatal period; psychological distress in only the postnatal period; and psychological distress in both the prenatal and postnatal periods.

The presence of AD was assessed by the mother using the International Study of Asthma and Allergies in Childhood (ISAAC) when the child was one and two years of age (Asher et al. 1995). The questionnaire consists of the following questions: 1) ‘Has your child ever had an itchy rash which was coming and going for at least six months?’; 2) ‘Has your child had this itchy rash at any time in the last 12 months?’; and 3) ‘Has this itchy rash at any time affected any of the following places: the folds of the elbows, behind the knees, in front of the ankles, under the buttocks, or around the neck, ears or eyes?’. If the answers to questions 2) and 3) were “yes”, AD was classified as “yes” (Odhiambo et al. 2009; Kuniyoshi et al. 2019). The development of AD was defined as the presence of AD in a 2-year-old child who had not had AD at the age of one year.

Potential confounders were selected based on a recent systematic review (Chan et al. 2018) and previous studies (Chiu et al. 2012; Brew et al. 2018). Maternal age at delivery was categorized into four age groups (18-29 years, 30-34 years, 35-39 years, ≥ 40 years). In early pregnancy (< 14 weeks) and one year after delivery, self-reported questionnaires were used to collect the following potential confounders: maternal smoking status in early pregnancy (never smoked, quit before becoming aware of pregnancy, quit after becoming aware of pregnancy, currently smoking), maternal educational attainment (high school or lower, junior or vocational college, university or higher), maternal history of AD (yes/no), and paternal history of AD (yes/no). Data on the maternal delivery and on the newborn child were collected from medical records, including parity (primipara, multipara), preterm birth (< 37, ≥ 37 weeks' gestation), low birth weight (< 2500 g, ≥ 2500 g), and child sex.

Differences in characteristics by maternal psychological distress were examined by using the chi-squared test. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated by multiple logistic regression analysis to examine the association between maternal psychological distress in the prenatal and postnatal periods and the development of AD in children. The analysis was

adjusted for the mothers' age at delivery, educational attainment, smoking status in pregnancy, history of AD, paternal history of AD, parity, child preterm birth, low birth weight, and sex.

Effect modifications were examined by multiple logistic regression analyses using cross-multiplied variables formed by maternal psychological distress and each potential confounder. There was no significant interaction for maternal psychological distress and each potential confounder ($p > 0.1$). Therefore, a stratified analysis was not conducted. All analyses were performed using SAS version 9.4 (SAS Inc., Cary, NC). A two-sided $p < 0.05$ was regarded as significant.

Results

Psychological distress was experienced in approximately half (46.8%, n = 3,971) of all women in the prenatal or postnatal period. This included 14.4% of women in only the prenatal period, 13.5% in only the postnatal period, and 19.0% in both periods. A total of 1,182 (13.9%) children developed AD between the ages of one and two years. Significant differences were observed in all variables except paternal history of AD, child preterm birth, and low birth weight (Table 1).

Table 2 shows the ORs and 95% CIs for the development of AD in children. Maternal psychological distress was associated with an increased risk of AD in children compared to no psychological distress in both periods (crude OR, 95% CI: 1.40, 1.19-1.64). This association remained after adjusting for potential confounders (adjusted OR, 95% CI: 1.41, 1.20-1.65). Maternal psychological distress in only the postnatal period was associated with an increased risk of AD in children compared to no psychological distress in both periods (crude OR, 95% CI: 1.27, 1.06-1.52). This association remained after adjusting for potential confounders (adjusted OR, 95% CI: 1.28, 1.06-1.54). Maternal psychological distress in only the prenatal period was not associated with an increased risk of AD in children compared to no psychological distress in both prenatal and postnatal periods (crude OR, 95% CI: 1.14, 0.95-1.37). This association remained after adjusting for potential confounders (adjusted OR, 95% CI: 1.15, 0.96-1.39). Maternal educational attainment, history of AD, paternal history of AD, and child sex were associated with AD in children, whereas mothers' age at delivery, smoking status in pregnancy, parity, child preterm birth, and low birth weight were not associated with AD in children.

Discussion

This study examined the association between cumulative exposure to maternal psychological distress in the prenatal and postnatal periods and the development of AD in children. Mothers with psychological distress in both the prenatal and postnatal periods and only the postnatal period were likely to have children with AD. The results suggest that continuous psychological distress in the prenatal and postnatal periods and that in only the postnatal period were risk factors for the development of AD in children.

Cumulative exposure to maternal psychological distress in the prenatal and postnatal periods was associated with an increased risk of AD in children. This is similar to the results reported by previous studies (Chiu et al. 2012; Brew et al. 2018). Chiu et al (2012) reported that the combined impact of high prenatal and postnatal maternal stress was associated with an increased risk of wheeze in children compared to low maternal stress in both periods (adjusted OR, 95% CI: 3.04, 1.67-5.53). Brew et al (2018) also found that cumulative exposure to maternal anxiety or depression in the prenatal and postnatal periods was associated with an increased risk of asthma in children compared to no anxiety or depression in both periods (adjusted OR, 95% CI: 1.50, 1.08-2.09). To the best of

my knowledge, this is the first study to examine the association between cumulative exposure to maternal psychological distress in the prenatal and postnatal periods and AD in children.

This consistency can be explained by the impact of each of prenatal and postnatal maternal psychological distress on AD in children. A systematic review reported that prenatal maternal mental health problems were associated with an increased risk of AD (Chan et al. 2018). Postnatal maternal mental health problems were also associated with an increased risk of AD (Wang et al. 2016; El-Heis et al. 2017; van der Leek et al. 2020). Therefore, cumulative exposure to maternal psychological distress in the prenatal and postnatal periods had a significant impact on AD in children. Biological mechanisms underlying the association between each of the prenatal and postnatal maternal mental health problems on AD need to be considered. In utero, maternal stress releases corticotropin-releasing hormone (CRH) via activation of the hypothalamic-pituitary-adrenal (HPA) axis (Faresjö 2015), and CRH is transported to the fetus through the placenta, which stimulates the fetal HPA axis to secrete glucocorticoids (Wright 2005). This modifies the infant's immune system (Faresjö 2015). It was also suggested the oxidative stress potentially

contributes to this mechanism (Chang et al. 2016). In the postnatal period, high maternal stress promotes immunoglobulin E expression and the allergen-specific proliferative response in the child. This changes immune functions and enhances the inflammatory response in the child (Wright et al. 2004). Additionally, distressed mother tend to lack cognitive function (Hakanen et al. 2019) and express rejection to the child (Hornstein et al. 2006; Letourneau et al. 2017). This may lead to low responsiveness to the child's needs or signals (Murray et al. 1996; Hornstein et al. 2006; Hakanen et al. 2019). Such a poor quality mother-infant interaction may increase the risk of AD (Letourneau et al. 2017). An animal study also demonstrated that low maternal responsiveness was significantly associated with a higher inflammatory stress response in the infant (Kinnally et al. 2019).

The results of the present study also supported previous studies that found an association between postnatal maternal mental health problems and AD in children (Wang et al. 2016; El-Heis et al. 2017; van der Leek et al. 2020). Therefore, a caregiver's psychological distress after delivery may be a trigger for AD to manifest in children.

Prenatal maternal psychological distress was not associated with an increased

risk of AD in children. This is inconsistent with most previous studies (Chan et al. 2018) that demonstrated an association between prenatal maternal mental health problems and the life or point prevalence of AD in children. This may be due to differences in the definition of outcomes. The onset of AD may be observed in early childhood in children with prenatally distressed mothers. A nationwide study reported that 17.0% of children manifested AD before one year of age, and the prevalence of AD at the age of one year was the highest in the first three years (Yamamoto-Hanada et al. 2020). In the present study, children who had AD at the age of one year were excluded. Therefore, the association between prenatal maternal psychological distress and AD might have not been evident.

This study has some implications for reducing the risk of AD in children. The results of this study suggest that cumulative exposure to maternal psychological distress in the prenatal and postnatal periods increases the risk of AD in children at the age of two years. This shows the importance of providing continuous support for mothers through the prenatal period to the postnatal period. In Japan, the government published a guideline from the prenatal and postnatal support project in 2017 (Ministry of Health, Labour and Welfare 2020). In 2019, the

government passed legislation requiring municipalities to make efforts to provide support for postpartum women (Ministry of Health, Labour and Welfare 2020). This project is expected to play a role in reducing mental health problems in high-risk mothers. A qualitative study showed that mothers experienced a lack of continuous care from the prenatal period to the postnatal period (Megnin-Viggars et al. 2015). In addition, some mothers were willing to receive education about pregnancy and the postpartum period from professionals, whereas others were unwilling to seek help from health care professionals unless their condition was serious (Nan et al. 2020). In that study, mothers were trying to solve problems by themselves. Apart from healthcare professionals, mothers' partners also play a significant role. A study reported that it is important that men be involved in the care before childbirth to enhance the couple's relationship and women's autonomy (Tokhi et al. 2018). Moreover, another study reported that support especially from partners may reduce the risk of AD in children (Letourneau et al. 2017).

The present study has several limitations. First, 35.7% of the participants in the TMM BirThree Cohort Study were included in this study. There were many missing data for maternal educational attainment, maternal and paternal histories

of AD, psychological distress, and child AD. This might happen because information about them was collected one or two years after delivery, and the follow-up rate had decreased. The participants included in the analysis were older and reported less distress, less smoking, fewer preterm and fewer low birth weight children than participants not included in the analysis (Table S1). Second, this study was conducted in one of the 47 prefectures in Japan. Therefore, the results of this study cannot be generalized. However, the TMM BirThree Cohort Study was able to recruit approximately half of the newborns in Miyagi Prefecture (Kuriyama et al. 2020). Last, maternal psychological distress and AD in children were assessed by self-reported questionnaires that may have led to misclassification. Self-reported AD in children might have been overestimated as demonstrated by a systematic review (Pols et al. 2016).

In conclusion, the present study found that cumulative exposure to maternal psychological distress in the prenatal and postnatal periods was associated with the development of AD in Japanese children at the age of two years. Continuous support from partners, family members, and society through the prenatal period to the postnatal period may be important to improve maternal psychological distress, which could potentially reduce the incidence of AD in children.

Acknowledgements

The author would like to thank all participants in the TMM BirThree Cohort Study. The author would also like to thank Professor Shinichi Kuriyama of the Department of Disaster Public Health of Tohoku University Graduate School of Medicine for his help in interpreting the results of this study. The author is also deeply grateful to Keiko Murakami for the courtesy of her excellent advice and support. The author would like to thank Taku Obara, Mami Ishikuro, Fumihiko Ueno, Aoi Noda, Tomomi Onuma for discussion regarding interpretation of this study. The author would also like to thank Masahiro Kikuya and Masako Miyashita for advice about the classification of AD, and Tomomi Onuma, Gen Oyanagi, and Mayumi Minami for support in the generation and utilization of the data. Moreover, the author would like to express gratitude to Daisuke Kikuchi, Misato Aizawa, Ippei Takahashi, Takahiro Yamashita, Yudai Yonezawa, Hisashi Ohseto, Takuma Usuzaki, the staff of the TMM BirThree Cohort Study and the secretaries of the department. Lastly, the author was greatly encouraged and supported by parents and friends through these postgraduate years.

Conflict of interest

There is no conflict of interest to declare.

References

American Psychological Association. (2020). APA Dictionary of Psychology. https://dictionary.apa.org/psychological-distress. Accessed 4th December 2020.

Asher, M.I., Keil, U., Anderson, H.R., Beasley, R., Crane, J., Martinez, F., Mitchell, E.A., Pearce, N., Sibbald, B., Stewart, A.W., Strachan, D., Weiland, S.K. & Williams, H.C. (1995). International Study of Asthma and Allergies in Childhood (ISAAC): Rationale and Methods. *Eur. Respir. J.,* **8**, 483–491.

Brew, B.K., Lundholm, C., Viktorin, A., Lichtenstein, P., Larsson, H. & Almqvist, C. (2018). Longitudinal Depression or Anxiety in Mothers and Offspring Asthma: A Swedish Populationbased Study. *Int. J. Epidemiol.,* **47**, 166–174.

Chan, C.W.H, Law, B.M.H., Liu, YH., Ambrocio, A.R.B, Au, N., Jiang, M. & Chow, K.M. (2018). The Association between Maternal Stress and Childhood Eczema: A Systematic Review. *Int. J. Environ. Res. Public Health.,* **15**, 395.

Chang, H.Y., Suh, D.I., Yang, SI., Kang, MJ., Lee, SY., Lee, E., Choi, I.A., Lee, KS., Shin, YJ., Shin, Y.H., Kim, Y.H, Kim, K.W., Ahn, K., Won, HS. & Choi, SJ. et al. (2016). Prenatal Maternal Distress Affects Atopic Dermatitis in Offspring Mediated by Oxidative Stress. *J. Allergy.Clin. Immunol.,* **138**,

468-475.

Chiu, YH.M., Coull, B.A., Cohen, S., Wooley, A. & Wright, R.J. (2012). Prenatal and Postnatal Maternal Stress and Wheeze in Urban Children. *Am. J. Respir. Crit. Care. Med.,* **186**, 147–154.

El-Heis, S., Crozier, S.R., Healy, E., Robinson, S.M., Harvey, N.C., Cooper, C., Inskip, H.M., Baird, J., Southampton Women's Survey Study Group. & Godfrey, K.M. (2017). Maternal stress and psychological distress preconception: association with offspring atopic eczema at age 12 months. *Clin. Exp. Allergy.,* **47**, 760–769.

Faresjö, M. (2015). The Link between Psychological Stress and Autoimmune Response in Children. *Crit. Rev. Immunol.,* **35**, 117–134.

Furukawa, T.A., Kawakami, N., Saitoh, M., Ono, Y., Nakane, Y., Nakamura, Y., Tachimori, H., Iwata, N., Uda, H., Nakane, H., Watanabe, M., Naganuma, Y., Hata, Y., Kobayashi, M. & Miyake, Y. et al. (2008). The performance of the Japanese version of the K6 and K10 in the World Mental Health Survey Japan. *Int. J. Methods Psychiatr. Res.,* **17**, 152–158.

Hakanen, H., Flykt, M., Sinervä, E., Nolvi, S., Kataja, EL., Pelto, J., Karlsson, H., Karlsson, L. & Korja, R. (2019). How maternal pre- and postnatal symptoms

of depression and anxiety affect early mother-infant interaction? *J. Affect. Disord.,* **257**, 83–90.

Hornstein, Ch., Trautmann-Villalba, P., Hohm, E., Rave, E., Wortmann-Fleischer, S. & Schwarz, M. (2006). Maternal bond and mother–child interaction in severe postpartum psychiatric disorders: Is there a link? *Arch. Womens. Ment. Health.,* **9**, 279–284.

Howlett, S. (1999). Emotional dysfunction, child-family relationships and childhood atopic dermatitis. *Br. J. Dermatol.,* **140**, 381–384.

Kessler, R.C., Andrews, G., Colpe, L.J., Hiripi, E., Mroczek, D.K., Normand, SL.T., Walters, E.E. & Zaslavsky, A.M. (2002). Short screening scales to monitor population prevalences and trends in non-specific psychological distress. *Psychol. Med.,* **32**, 959–976.

Kinnally, E.L., Martinez, S.J., Chun, K., Capitanio, J.P. & Ceniceros, L.C. (2019). Early Social Stress Promotes Inflammation and Disease Risk in Rhesus Monkeys. *Sci. Rep.,* **9**, 1–8.

Kuniyoshi, Y., Kikuya, M., Miyashita, M., Yamanaka, C., Ishikuro, M., Obara, T., Metoki, H., Nakaya, N., Nagami, F., Tomita, H., Hozawa, A., Tsuji, I., Kure, S., Yaegashi, N. & Shinichi, K. (2019). Prefabricated Temporary Housing

and Eczema or Respiratory Symptoms in Schoolchildren after the Great East Japan Earthquake: The ToMMo Child Health Study. *Disaster. Med. Public. Health. Prep.,* **13**, 905–911.

Kuriyama, S, Metoki, H., Kikuya, M., Obara, T., Ishikuro, M., Yamanaka, C., Nagai, M., Matsubara, H., Kobayashi, T., Sugawara, J., Tamiya, G., Hozawa, A., Nakaya, N., Tsuchiya, N. & Nakamura, T. et al. (2020). Cohort Profile: Tohoku Medical Megabank Project Birth and Three-Generation Cohort Study (TMM BirThree Cohort Study): Rationale, Progress and Perspective. *Int. J. Epidemiol.,* **49**, 1-15.

Letourneau, N.L., Kozyrskyj, A.L., Cosic, N., Ntanda, H.N., Anis, L., Hart, M.J., Campbell, T.S., Giesbrecht, G.F. & The APrON Team. (2017). Maternal sensitivity and social support protect against childhood atopic dermatitis. *Allergy. Asthma. Clin. Immunol.,* **13**, 1-14.

Megnin-Viggars, O., Symington, I., Howard, L.M. & Pilling, S. (2015). Experience of care for mental health problems in the antenatal or postnatal period for women in the UK: a systematic review and meta-synthesis of qualitative research. *Arch. Womens. Ment. Health.,* **18**, 745–759.

Ministry of Health, Labour and Welfare. (2020). Prenatal and Postnatal Support

Project Guideline. https://www.mhlw.go.jp/content/000658063.pdf. Accessed 8th December 2020.

Mora, P.A., Bennett, I.M., Elo, I.T., Mathew, L., Coyne, J.C. & Culhane, J.F. (2009). Distinct Trajectories of Perinatal Depressive Symptomatology: Evidence from Growth Mixture Modeling. *Am. J. Epidemiol.,* **169**, 24–32.

Murray, L., Fiori-Cowley, A., Hooper, R & Cooper, P. (1996). The Impact of Postnatal Depression and Associated Adversity on Early Mother-Infant Interactions and Later Infant Outcome. *Child. Dev.,* **67**, 2512–2526.

Nan, Y., Zhang, J., Nisar, A., Huo, L., Yang, L., Yin, J., Wang, D., Rahman, A., Gao, Y. & Li, X. (2020). Professional support during the postpartum period: primiparous mothers' views on professional services and their expectations, and barriers to utilizing professional help. *BMC Pregnancy Childbirth.,* **20**, 1–13.

Odhiambo, J.A., Williams, H.C., Clayton, T.O., Robertson, C.F., Asher, M.I. & the ISAAC Phase Three Study Group. (2009). Global variations in prevalence of eczema symptoms in children from ISAAC Phase Three. *J. Allergy. Clin. Immunol.,* **124**, 1251-1258.

Pols, D.H.J., Wartna, J.B., Moed, H., van Alphen, E.I., Bohnen, A.M. & Bindels,

P.J.E. (2016). Atopic dermatitis, asthma and allergic rhinitis in general practice and the open population: a systematic review. *Scand. J. Prim. Health. Care.,* **34**, 143–150.

Rotheram-Fuller, E.J., Tomlinson, M., Scheffler, A., Weichle, T.W., Rezvan, P.H., Comulada, W.S. & Rotheram-Borus, J. (2018). Maternal Patterns of Antenatal and Postnatal Depressed Mood and the Impact on Child Health at 3-Years Postpartum. *J. Consult. Clin. Psychol.,* **86**, 218–230.

Sakurai, K., Nishi, A., Kondo, K., Yanagida, K. & Kawakami, N. (2011). Screening performance of K6/K10 and other screening instruments for mood and anxiety disorders in Japan. *Psychiatry. Clin. Neurosci.,* **65**, 434–441.

Sutter-Dallay, A.L., Cosnefroy, O., Glatigny-Dallay, E., Verdoux, H. & Rascle, N. (2012). Evolution of perinatal depressive symptoms from pregnancy to two years postpartum in a low-risk sample: The MATQUID cohort. *J. Affect. Disord.,* **139**, 23–29.

Tokhi, M., Comrie-Thomson, L., Davis, J., Portela, A., Chersich, M. & Luchters, S. (2018). Involving men to improve maternal and newborn health: A systematic review of the effectiveness of interventions. *PLoS ONE.,* **13**, 1-16.

van der Leek, A.P., Bahreinian, S., Chartier, M., Dahl, M.E., Azad, M.B., Brownell, M.D. & Kozyrskyj, A.L. (2020). Maternal Distress During Pregnancy and Recurrence in Early Childhood Predicts Atopic Dermatitis and Asthma in Childhood. *Chest.,* **158**, 57-67.

Wang, I.J., Wen, H.J., Chiang, T.L., Lin, S.J. & Guo, Y.L. (2016). Maternal psychologic problems increased the risk of childhood atopic dermatitis. *Pediatr. Allergy. Immunol.,* **27**, 169–176.

Weidinger, S. & Novak, N. (2016). Atopic dermatitis. *Lancet.,* **387**, 1109–1122.

Wright, R.J. (2005). Stress and atopic disorders. *J. Allergy. Clin. Immunol.,* **116**, 1301–1306.

Wright, R.J., Finn, P., Contreras, J.P., Cohen, S., Wright, R.O., Staudenmayer, J., Wand, M., Perkins, D., Weiss, S.T. & Gold, D.R. (2004). Chronic caregiver stress and IgE expression, allergen-induced proliferation, and cytokine profiles in a birth cohort predisposed to atopy. *J. Allergy. Clin. Immunol.,* **113**, 1051–1057.

Yamamoto-Hanada, K., Pak, K., Saito-Abe, M., Yang, L., Sato, M., Irahara, M., Mezawa, H., Sasaki, H., Nishizato, M., Ishitsuka, K. & Ohya, Y. (2020). Allergy and immunology in young children of Japan: The JECS cohort. *World.*

398 *Allergy. Organ. J.,* **13**, 1-14.

399 Yang, E.J., Beck, K.M., Sekhon, S., Bhutani, T. & Koo, J. (2019). The impact of

400 pediatric atopic dermatitis on families: A review. *Pediatr. Dermatol.,* **36**, 66–

401 71.

Figure

Figure 1. Flow diagram of participants in this study

[a]Data on smoking status and prenatal psychological distress were obtained from the questionnaire in early pregnancy (< 14 weeks).

[b]Data on parity, child birth weight, and gestational age were obtained from the medical record.

[c]Data on postnatal psychological distress, educational attainment, and maternal and paternal histories of AD were obtained from the questionnaire at one year after delivery.

[d]Data on child AD at the age of one year were obtained from the questionnaire at the age of one year.

[e]Data on child AD at the age of two years were obtained from the questionnaire at the age of two years.

AD = Atopic Dermatitis

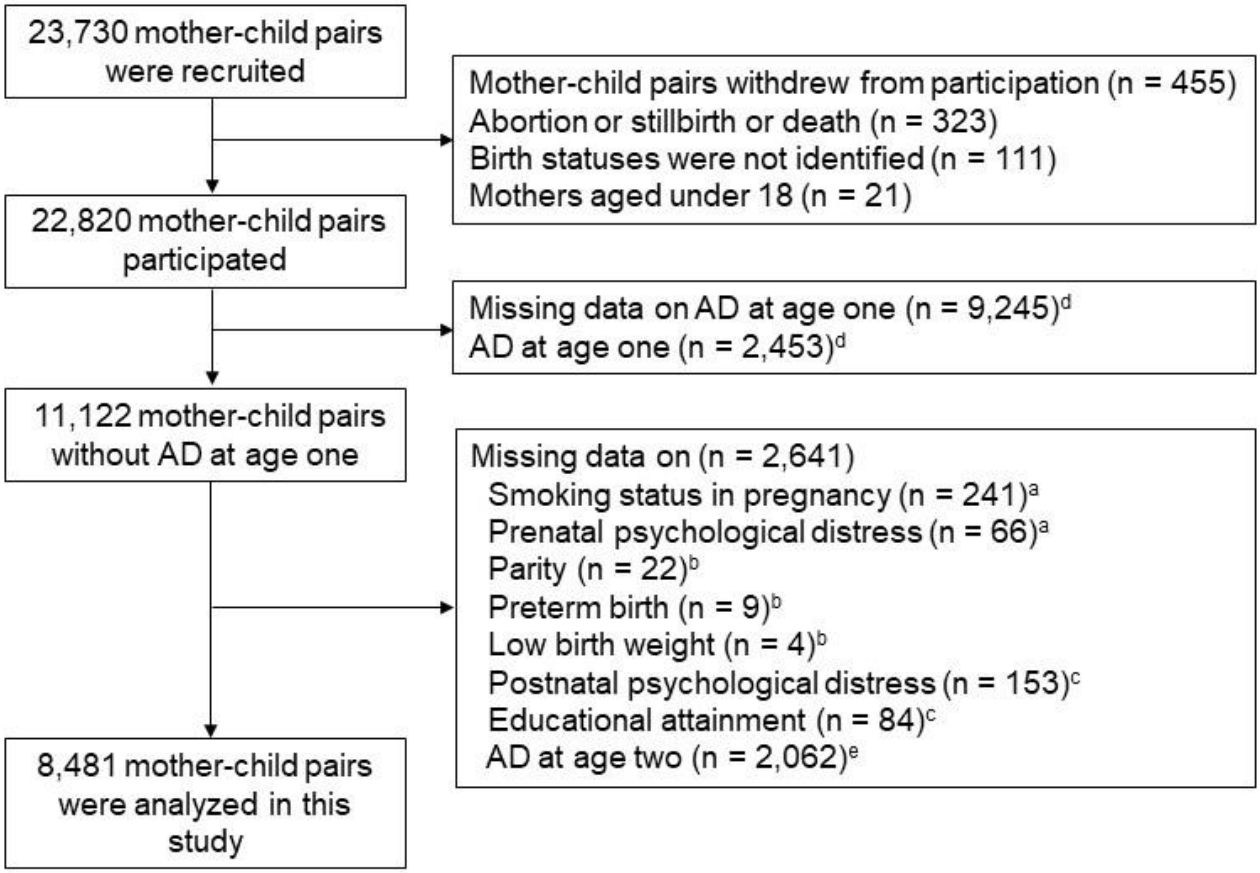

Figure 1. Flow diagram of participants in this study

AD = Atopic Dermatitis

Tables

Table 1. Characteristics of participants by maternal psychological distress

	Total (n = 8,481) n (%)	Maternal psychological distress n (%)				P-value*
		None (n = 4,510)	Prenatal only (n = 1,217)	Postnatal only (n = 1,144)	Both (n = 1,610)	
Age at delivery						< 0.0001
18-29 years	2209 (26.1)	1032 (22.9)	360 (29.6)	281 (24.6)	536 (33.3)	
30-34 years	3239 (38.2)	1711 (37.9)	466 (38.3)	466 (40.7)	596 (37.0)	
35-39 years	2326 (27.4)	1336 (29.6)	289 (23.8)	327 (28.6)	374 (23.2)	
≥ 40 years	707 (8.3)	431 (9.6)	102 (8.4)	70 (6.1)	104 (6.5)	
Educational attainment						< 0.0001
High school or lower	2716 (32.0)	1334 (29.6)	406 (33.4)	392 (34.3)	584 (36.3)	
Junior or vocational college	3303 (39.0)	1815 (40.2)	470 (38.6)	427 (37.3)	591 (36.7)	
University or higher	2462 (29.0)	1361 (30.2)	341 (28.0)	325 (28.4)	435 (27.0)	
Smoking status in pregnancy						< 0.0001
Never smoked	5442 (64.2)	3016 (66.9)	758 (62.3)	751 (65.7)	917 (57.0)	
Quit smoking before pregnancy	1981 (23.4)	1018 (22.6)	281 (23.1)	267 (23.3)	415 (25.8)	
Quit smoking after pregnancy	917 (10.8)	426 (9.5)	159 (13.1)	102 (8.9)	230 (14.3)	
Currently smoking	141 (1.7)	50 (1.1)	19 (1.6)	24 (2.1)	48 (3.0)	
Maternal history of AD						0.0019
No	7454 (87.9)	4008 (88.9)	1058 (86.9)	1013 (88.6)	1375 (85.4)	
Yes	1027 (12.1)	502 (11.1)	159 (13.1)	131 (11.5)	235 (14.6)	
Paternal history of AD						0.70
No	7927 (93.5)	4223 (93.6)	1132 (93.0)	1074 (93.9)	1498 (93.0)	
Yes	554 (6.5)	287 (6.4)	85 (7.0)	70 (6.1)	112 (7.0)	
Parity						< 0.0001
Primipara	3971 (46.8)	2000 (44.4)	649 (53.3)	503 (44.0)	819 (50.9)	
Multipara	4510 (53.2)	2510 (55.7)	568 (46.7)	641 (56.0)	791 (49.1)	
Sex						0.032
Female	4165 (49.1)	2158 (47.9)	615 (50.5)	557 (48.7)	835 (51.9)	
Male	4316 (50.9)	2352 (52.2)	602 (49.5)	587 (51.3)	775 (48.1)	
Preterm birth						0.19
No	7972 (94.0)	4252 (94.3)	1130 (92.9)	1069 (93.4)	1521 (94.5)	
Yes	509 (6.0)	258 (5.7)	87 (7.2)	75 (6.6)	89 (5.5)	
Low birth weight						0.091
No	7671 (90.4)	4098 (90.9)	1077 (88.5)	1039 (90.8)	1457 (90.5)	
Yes	810 (9.6)	412 (9.1)	140 (11.5)	105 (9.2)	153 (9.5)	
Development of AD at the age of two years						0.0002
No	7299 (86.1)	3944 (87.5)	1046 (86.0)	968 (84.6)	1341 (83.3)	
Yes	1182 (13.9)	566 (12.6)	171 (14.1)	176 (15.4)	269 (16.7)	

*Obtained using the chi-squared test/ AD = Atopic Dermatitis

Table 2. The association between maternal psychological distress and the development of AD in children at the age of two years

	Development of AD/ mother-child pairs	%	Crude OR (95% CI)	Adjusted OR (95% CI)*
Maternal psychological distress				
None in both prenatal and postnatal	566/4510	12.5	1.00	1.00
Prenatal only	171/1217	14.1	1.14 (0.95–1.37)	1.15 (0.96–1.39)
Postnatal only	176/1144	15.4	1.27 (1.06–1.52)	1.28 (1.06–1.54)
Both in prenatal and postnatal	269/1610	16.7	1.40 (1.19–1.64)	1.41 (1.20–1.65)
Age at delivery				
18-29 years	294/2209	13.3	1.00	1.00
30-34 years	462/3239	14.3	1.11 (0.94–1.29)	1.04 (0.89–1.23)
35-39 years	335/2326	14.4	1.13 (0.95–1.34)	1.07 (0.90–1.28)
≥ 40 years	91/707	12.9	1.01 (0.78–1.29)	1.00 (0.77–1.29)
Educational attainment				
High school or lower	338/2716	12.4	1.00	1.00
Junior or vocational college	463/3303	14.0	1.17 (1.00–1.36)	1.15 (0.99–1.35)
University or higher	381/2462	15.5	1.31 (1.12–1.54)	1.30 (1.10–1.54)
Smoking status in pregnancy				
Never smoked	742/5442	13.6	1.00	1.00
Quit smoking before pregnancy	299/1981	15.1	1.11 (0.96–1.29)	1.12 (0.97–1.30)
Quit smoking after pregnancy	121/917	13.2	0.94 (0.76–1.15)	1.00 (0.81–1.24)
Currently smoking	20/141	14.2	0.98 (0.61–1.59)	1.13 (0.70–1.85)
Maternal history of AD				
No	983/7454	13.2	1.00	1.00
Yes	199/1027	19.4	1.56 (1.32–1.85)	1.52 (1.28–1.80)
Paternal history of AD				
No	1058/7927	13.4	1.00	1.00
Yes	124/554	22.4	1.87 (1.51–2.31)	1.79 (1.45–2.21)
Parity				
Primipara	541/3971	13.6	1.00	1.00
Multipara	641/4510	14.2	1.06 (0.94–1.20)	1.09 (0.96–1.24)
Sex				
Female	537/4165	12.9	1.00	1.00
Male	645/4316	14.9	1.20 (1.06–1.35)	1.21 (1.07–1.37)
Preterm birth				
No	1107/7972	13.9	1.00	1.00
Yes	75/509	14.7	1.07 (0.83–1.38)	1.10 (0.82–1.47)
Low birth weight				
No	1071/7671	14.0	1.00	1.00
Yes	111/810	13.7	0.98 (0.79–1.21)	0.93 (0.73–1.19)

*Adjusted for all other variables in the table.

AD = Atopic Dermatitis, OR = Odds Ratio, CI = Confidence Interval

Supplement

Table S1. Characteristics of participants included and not included in the analysis

	Participants included (n = 8,481), n (%)	Participants not included (n = 15,249), n (%)
Age at delivery		
18-29 years	2209 (26.1)	4814 (33.1)
30-34 years	3239 (38.2)	5187 (35.6)
35-39 years	2326 (27.4)	3506 (24.1)
≥ 40 years	707 (8.3)	1049 (7.2)
Educational attainment		
High school or lower	2716 (32.0)	1947 (34.4)
Junior or vocational college	3303 (39.0)	2162 (38.2)
University or higher	2462 (29.0)	1555 (27.5)
Smoking status in pregnancy		
Never smoked	5442 (64.2)	7787 (57.1)
Quit smoking before pregnancy	1981 (23.4)	3213 (23.5)
Quit smoking after pregnancy	917 (10.8)	2227 (16.3)
Currently smoking	141 (1.7)	418 (3.1)
Maternal history of AD		
No	7454 (87.9)	4850 (83.6)
Yes	1027 (12.1)	952 (16.4)
Paternal history of AD		
No	7927 (93.5)	5280 (91.0)
Yes	554 (6.5)	522 (9.0)
Perinatal psychological distress		
None in both prenatal and postnatal	4510 (53.2)	2590 (48.4)
Prenatal only	1217 (14.4)	764 (14.3)
Postnatal only	1144 (13.5)	841 (15.7)
Both in prenatal and postnatal	1610 (19.0)	1156 (21.6)
Parity		
Primipara	3971 (46.8)	6847 (47.0)
Multipara	4510 (53.2)	7732 (53.0)
Sex		
Female	4165 (49.1)	6988 (45.8)
Male	4316 (50.9)	8261 (54.2)
Preterm birth		
No	7972 (94.0)	13310 (91.3)
Yes	509 (6.0)	1275 (8.7)
Low birth weight		
No	7671 (90.4)	12873 (88.3)
Yes	810 (9.6)	1701 (11.7)
Development of AD at the age of two years		
No	7299 (86.1)	380 (87.0)
Yes	1182 (13.9)	57 (13.0)

Percentages were calculated after excluding missing values.
AD = Atopic Dermatitis